

# Comparative outcomes of lopinavir/ritonavir and hydroxychloroquine for the treatment of coronavirus disease 2019 with mild to moderate severity.

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## Research Article

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# Abstract

**Background:** Lopinavir/ritonavir and hydroxychloroquine are both being used to treat COVID-19, but their relative effectiveness is unknown. The purpose of this study was to compare the clinical outcomes of patients treated for COVID-19 with lopinavir/ritonavir (LPV/r) or hydroxychloroquine (HCQ).

**Methods:** A retrospective cohort study was conducted at 2 hospitals in Busan, South Korea, that treated approximately 90% of COVID-19 patients hospitalized in Busan during the study period. All patients aged  $\geq 15$  years that were hospitalized with mild-or-moderate COVID-19 received LPV/r or HCQ as their initial treatment and were included in the analysis.

**Results:** Among the 72 patients with mild-to-moderate disease severity on admission, 45 received LPV/r and 27 received HCQ as their initial therapy. A higher proportion of the LPV group had pneumonia on admission (LPV 49% vs. HCQ 15%), but there were no other significant differences in the demographic or clinical characteristics between groups.

Switching therapy due to clinical failure was significantly more common in the HCQ group than in the LPV/r group (41% [11/27] and 2% [1/45], respectively,  $P=0.001$ ). Disease progression was also significantly more common in the HCQ group than in the LPV/r group (44% [12/27] and 18% [8/45], respectively,  $P=0.030$ ).

**Conclusions:** LPV/r appears to be more effective than HCQ at preventing progression to severe disease in patients with COVID-19.

## Background

Coronavirus disease-19 (COVID-19) is an emerging, highly infectious disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It first appeared in Wuhan, Hubei Province, China, in December 2019 and rapidly spread globally and on March 11, 2020, World Health Organization (WHO) declared COVID-19 a pandemic [1-5].

An analysis of 72,314 cases from China, revealed that most patients experienced mild disease, with 14% developing severe disease, and 5% developing critical disease, and the case fatality rate was 2.3% [6]. About 50% of patients with critical disease died, and the mortality rate was high in patients over the age of 70 years and those with pre-existing comorbidities. In other study, of 52 critically ill patients with SARS-CoV-2 infection, 62% died within 28 days [7]. Given the high mortality rate in critically ill patients, effective antiviral treatment, especially when administered early to patients at risk of developing severe disease, may improve the clinical outcomes of COVID-19.

There is currently no standard antiviral therapy for COVID-19 so treatment is supportive. Existing antiviral agents have been repurposed and prescribed for treatment of COVID-19 based on therapeutic experience

with 2 other infections caused by human coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV), and middle east respiratory syndrome coronavirus (MERS-CoV) [8].

Lopinavir/ritonavir (LPV/r) is a protease inhibitor that is used to treat human immunodeficiency virus (HIV) infection. It has been hypothesized that this combination drug may inhibit the protease of MERS-CoV and SARS-CoV, thus blocking the processing of the viral replicase polyprotein and preventing the replication of viral ribonucleic acid (RNA) [8,9], however, it is controversial whether HIV protease inhibitors could effectively inhibit the protease of SARS-CoV-2 [8]. A non-randomized, open-label trial revealed that, among patients with SARS, patients treated with LPV/r (n=41) experienced fewer adverse clinical outcomes (acute respiratory distress syndrome or death) than those treated with ribavirin alone (n=111) (2.4% versus 28.8%,  $p < 0.001$ ) [10]. In previous MERS outbreak, LPV was reported to have antiviral activity in vitro and in vivo and Chan et al [11]. demonstrated that treatment of animals infected with MERS-CoV with LPV/r improved the clinical outcomes and reduced viral loads in lung and most extra-pulmonary tissue. However, another in vivo study showed that therapeutic effect of LPV/r and interferon beta did not reduce viral replication [12]. A recent case report demonstrated that treatment of SARS-CoV-2 infection with LPV/r was associated with a reduction in the viral load and improved clinical symptoms; however, there have been no clinical studies to date that have provided evidence to support the use of LPV/r as treatment for SARS-CoV-2 [13].

Chloroquine/hydroxychloroquine (HCQ), a drug that is widely used as an anti-malarial and for the treatment of autoimmune disease, exerts direct antiviral effects, inhibiting pH- dependent steps of the replication of several viruses, including coronaviruses [14]. Moreover, chloroquine has immunomodulatory effects, and reduces the production/release of tumor necrosis factor alpha and interleukin-6, which mediate the inflammatory complication of viral disease.[14] In an in vitro study, chloroquine was found to have antiviral activity against SARS-CoV and MERS-CoV [15-17]. Recently, chloroquine/HCQ has been shown to inhibit the growth of SARS-CoV-2 in vitro, and clinical studies are in progress [18, 19].

Both LPV/r and HCQ have been used long-term, are relatively tolerable, and their pharmacokinetics, pharmacodynamics, side effects are well known, so prescription can be considered in patients with early, mild COVID-19. There is a question of whether an early administration of antiviral agent can reduce the progression to severe COVID-19 infection or improve the overall course of treatment, but there have been no studies to date. The aim of this study was to evaluate the clinical outcomes of early antiviral treatment and to compare LPV/r and HCQ for treatment of mild COVID-19.

## Methods

### Study design, setting, and participants.

We conducted a retrospective cohort study at Pusan National University Hospital (PNUH) and Busan Medical Center (BMC) in Busan, South Korea. Busan is a metropolitan city with a population of more than 3 million people. PNUH and BMC are the only hospitals in Busan designated to treat patients with COVID-

19. A COVID-19 outbreak was detected in Busan on 21 February 2020. The Busan health authority referred most patients with confirmed COVID-19 to PNUH and BMC on a non-selective basis. We enrolled patients who were admitted to two hospitals from February 21, 2020 to March 21, 2020, and observed patients until April 3, 2020. All patients were hospitalized for their entire disease period from diagnosis to recovery and discharge and their clinical progress was monitored. In PNUH, LPV/r was administered to almost all patients regardless of the severity of disease. In BMC, HCQ was administered to patients with mild illness, without comorbidities, as the primary antiviral agent, and LPV/r was administered to people with comorbidities or pneumonia at presentation. Generally, patients treated with HCQ were switched to LPV/r if their clinical condition worsened (Fig. 1).

All adult patients ( $\geq 15$  years) with confirmed COVID-19 who received LPV/r (400/100 mg orally every 12 hours) or HCQ (400 mg orally every 24 hours) as initial antiviral treatment were enrolled in this study. We excluded patients who had severe disease who required oxygen supplementation or mechanical ventilation at the time of diagnosis and patients who did not live in Busan.

### **Data collection procedure**

We extracted epidemiological, demographic, clinical, laboratory, and outcome data from patient's electronic medical records using a standardized data collection form. All data were checked by 2 physicians (S Lee and J Heo) and a third physician (SO Lee) adjudicated any difference in interpretation.

To diagnose SARS-CoV-2 infection, oropharyngeal, nasopharyngeal swab and sputum specimens were obtained from all patients and tested using real-time transcriptase-polymerase chain reaction (RT-PCR) assays according to protocol, at public health centers or laboratory centers certified by the Korean Centers for Disease Control and Prevention (KCDC) before admission. The definition for cure was 48 hours after all symptoms disappeared, and 2 oropharyngeal/nasopharyngeal swab and sputum samples, obtained at least 24 hours apart, negative for SARS-CoV-2 RNA. Additionally, patients underwent routine blood testing (including complete blood count, coagulation profile, serum biochemical test, myocardial enzymes, C-reactive protein and procalcitonin) and chest X-rays or computer tomography. The frequency and timing of the tests was determined by the attending physicians.

### **Outcomes**

Patients were assigned to the LPV/r group or the HCQ group based on the initial antiviral agents with which they were treated. The main outcome was progression of clinical disease. The progression of clinical disease was defined as exacerbation of any category of clinical syndrome associated COVID-19, as described in the World Health Organization interim guidance.[20] The 6 categories in order of increasing severity were: (1) Uncomplicated illness; (2) Mild pneumonia, (3) Severe pneumonia, (4) Acute respiratory distress syndrome (ARDS), (5) Sepsis, and (6) Septic shock. We also compared the development of pneumonia and progression of disease that require mechanical ventilation between 2 groups as secondary outcomes.

## Statistical analysis

R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, and continuous variables were tested using the Kruskal–Wallis test. All tests of significance were 2-tailed;  $p < 0.05$  was considered to be significant.

## Results

### COVID-19 epidemics in Busan

During the 3-week study period, about 48,000 confirmation tests of COVID-19 were performed in Busan during 3 weeks and 92 adults ( $\geq 15$  years) were diagnosed with COVID-19. Among the 92 confirmed COVID-19 patients, 81 were hospitalized in PNUH or BMC. Their median age was 35 years (interquartile range [IQR]: 24–55 years) and 37 (46%) were male. Seven patients (10%) were asymptomatic at the time of diagnosis. Among the symptomatic patients, 85% were diagnosed within 5 days of symptom onset; and the median time from onset to diagnosis was 3 days (IQR: 1–5 days). At the time of diagnosis, 54 patients (67%) had uncomplicated illness (WHO class 1), 26 (32%) had mild pneumonia (WHO class 2) and 1 (1%) had acute respiratory distress syndrome (WHO class 4).

### Clinical characteristics

Among the 81 hospitalized COVID-19 patients, 72 patients who had mild-to-moderate severity disease and received LPV/r or HCQ as the initial antiviral agents were included in this analysis. Their demographic and clinical characteristics on admission are summarized in Table 1. Their median age was 37 years (IQR: 24–55 years), and 44% of the patients were male. The patients received antiviral agents within median of 3 (IQR: 2–5) days after symptom onset. Of the 72 patients, 45 (63%) received LPV/r as the initial antiviral treatment and 27 (38%) received HCQ. There was no significant difference between the patients in the 2 treatment groups in terms of demographic characteristics, vital signs on presentation, or comorbidities on admission. However, patients with pneumonia were significantly more likely to receive LPV/r than HCQ as the initial antiviral therapy. The prevalence of pneumonia was 49% (20/45) in the LPV/r group and 15% (4/27) in the HCQ group ( $P=0.008$ ).

### Early antiviral treatment outcomes of COVID-19

The treatment outcomes are shown in Table 2. The rate of switching antiviral agents within 7 days because of clinical failure was 2% (1/45) in the LPV/r group and 41% (11/27) in the HCQ group ( $P < 0.001$ ). Eight patients (18%) in the LPV/r group and 12 patients (44%) in the HCQ group experienced clinical progression ( $P=0.030$ ).

In a subgroup analysis of WHO class 1 patients, 44% (10/23) of patients who initially received HCQ, and none of the patients who initially received LPV/r had their antiviral therapy modified by the attending

physician ( $P=0.002$ ). Eleven patients in the LPV/r group (48%) and 7 patients in HCQ group (30%) developed pneumonia during therapy ( $P=0.37$ ).

### **Outcomes of LPV/r in patients with COVID-19 pneumonia**

Forty-five (63%) of the patients hospitalized with COVID-19 developed pneumonia. Twenty-seven patients (38%) were diagnosed with pneumonia at the time of presentation and 18 patients (25%) were diagnosed with pneumonia during the course of antiviral therapy.

Among the 45 patients with COVID-19 pneumonia, 41 (91%) were treated with LPV/r; 30 (67%) as primary therapy and 11 (25%) as salvage therapy after primary HCQ therapy.

Among the patients who received LPV/r, 9 (22%) were over 70 years old. Thirty-two patients (78%) had multifocal lesions, 28 (68%) had bilateral lesions, and 4 (10%) had diffuse bilateral pneumonia.

Among the 45 patients with COVID-19 pneumonia who received LPV/r, 38 (93%) recovered without oxygen supplementation or mechanical ventilator therapy. Three patients needed mechanical ventilation. Two patients with WHO class 3 and 4 severity at initiation of LPV/r and one patient initiated LPV/r for mild COVID-19 developed severe disease requiring ventilator therapy. Of the 3 patients treated using a mechanical ventilator, one was cured but the other 2 died due to exacerbation of COVID-19 pneumonia.

## **Discussion**

The incidence of COVID-19 is high in many countries globally, and the number of patients with severe disease requiring mechanical ventilation is also rapidly increasing. The number of deaths is increasing due to a lack of sufficient critical care facilities and equipment such as mechanical ventilators.

Conducting clinical trials to determine the efficacy of new drugs, and licensing new drugs takes time. Even drugs that are known to have therapeutic effects require comparative studies on the therapeutic effects in various clinical situations. Patient with COVID-19 of mild-to-moderate severity on presentation may be cured without complications or may progress to severe and debilitating disease. Clinical information is needed to determine whether administration of antiviral agents early in the course of disease can reduce the incidence of severe cases requiring oxygen supplementation or mechanical ventilation. However, most of the information currently available is based on studies of patients who have already had severe disease on admission [21]. The results of this study provide some useful information regarding.

First, our study suggests that early administration of antiviral agent, especially LPV/r to the COVID-19 patients with mild-to-moderate severity can reduce the exacerbation of the disease to severe cases which need oxygen supplementation and mechanical ventilator therapy. One of the largest epidemiologic study from China reported that, among 72,314 COVID-19 cases, 14% were severe and 5% were critical [6]. Guan et al.[22] reported that proportion of severe disease was 15.7%.

In the clinical progression to severe in COVID-19 infection, the median duration from symptoms to dyspnea was 8 days, to ARDS was 9 days, to intensive care unit admission and mechanical ventilation was 10.5 days [2]. In our study, about 90 % of patients with COVID-19 in Busan were hospitalized in the 2 study hospitals and most of them initiated antiviral drugs early before exacerbation of their COVID-19; from symptom onset to antiviral administration was 3 days. Considering the clinical course of COVID-19, antiviral drugs were administered relatively early in our study and 96% of patients did not need oxygen supplementation or mechanical ventilation. Only 4% of patients required mechanical ventilation. Compared to the result of the study from China, the proportion of severe patients in our study was low although our study included considerable number of elderly patients and patients with significant extent of pneumonia [6]. Therefore, our findings suggest that early diagnosis and early administration of antiviral agent for COVID-19 may reduce the incidence of progression to severe disease and may be associated with better outcomes than if administration of antiviral agents is reserved for patients with severe and complicated disease.

Second, our study demonstrated that patients who received LPV/r were less likely to experience disease progression than those who received HCQ when the antiviral agents were administered early to patients with uncomplicated illness or mild pneumonia, and that these patients were rarely switched to a secondary drug. Conversely, 40% of the patients who were initially treated with HCQ, were switched to LPV/r as salvage therapy due to the attending physician judging that the patient had treatment failure. Although not statistically significant, newly developed pneumonia was also less frequent in patients who received LPV/r than those who received HCQ. It is also noteworthy that the patients receiving LPV/r as the initial antiviral agent had relatively more severe disease and more comorbidities than the patients who were treated with HCQ, suggesting that physicians had a tendency to select LPV/r for patients who were in poorer clinical condition. This might have masked the possible benefits of LPV/r treatment.

A recent randomized controlled trial demonstrated that LPV/r treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with severe COVID-19 [21]. However, in this study, the median interval from symptom onset to initiation of antiviral therapy was 13 days, and it is possible that the LPV/r treatment was initiated after clinical deterioration [21]. In a study of use of LPV/r in patients with SARS, LPV/r was associated with reduced steroid use, a reduced need for mechanical ventilation and lower mortality when it was administered in the early stage, but did not show a therapeutic effect if treatment was initiated later in the course of disease [23]. Based on these findings, we hypothesize that early LPV/r treatment for COVID-19, can improve clinical outcomes although LPV/r does not appear to have a clinically significant effect in patients with severe COVID-19.

Some recent studies have shown that HCQ is a potent inhibitor for SARS-CoV-2 in vitro [19, 24]. A recent open label trial which was conducted in France demonstrated that HCQ is significantly associated with viral load reduction in patients with mild COVID-19 and the researchers concluded that HCQ is a promising antiviral agent for COVID-19 [25]. However, in our study, HCQ compared to LPV/r did not effectively prevent clinical progression of COVID-19, and about 40% of patients who receiving HCQ had their antiviral agent switched due to clinically diagnosed failure. To date, no controlled trials of HCQ for

SARS-CoV-2 infection have reported clinical outcomes other than a reduction of viral load. Further research is warranted to confirm the clinical effects of HCQ.

Third, our study suggested that LPV/r could be used without major side effects in mild COVID-19 infection. The safety of LPV/r has been confirmed in individuals with HIV- infection, and LPV/r has been used to treat HIV infection for a long time. Known side effects of LPV/r include diarrhea, abnormal stools, abdominal pain, nausea, vomiting, and asthenia [26]. In our study, 22 patients (49%) in the LPV/r group experienced adverse effects, and 2 patients (4%) interrupted drug due to adverse effects. One patient stopped LPV/r because of skin rash, and the other patient stopped LPV/r because of loss of the sense of taste. No life- threatening side effects have been identified in mild patients.

Our study has some limitations. First, the patients who enrolled our study were not randomly assigned to LPV/r group and HCQ group because our study was an observational study.

Therefore, attending physicians' prior knowledge or preconceptions of antiviral agents may have influenced their choice of antiviral agent, and led them to prescribe LPV/r for more severe cases. Although the patients were not randomized assigned to LPV/r group and HCQ group, the Busan city government distributed patients with confirmed COVID-19 patients to the 2 hospitals on a non-selective basis, and treatment practices differed by hospital, regardless of severity. This reduced the probability of that relatively serious patients would preferentially receive LPV/r because PNUH used LPV/r as the initial antiviral agent in almost all patients.

Second, there was no uniform protocol in our study because our study was not an experimental study. Therefore, the standard of care may have differed between the 2 hospitals. However, the staff at both hospitals had to follow the guidelines of KCDC and the Busan city government that all patients with confirmed COVID-19 should be hospitalized in the isolation wards; that their clinical course should be observed during hospitalization; and that they should be use the criteria of KCDC to decide when patients were cured and could be released from isolation. Therefore, the entire treatment period was observed in an isolated ward even though some patients had only mild symptoms. This allowed the clinical effects of 2 drugs to be compared in settings similar to experimental study, despite the lack of a uniform protocol.

Third, in this study, HCQ was administered orally at 400 mg daily based on South Korean expert recommendations. However, other studies have shown that 200 mg 8-hourly or 200 mg 12-hourly after a loading dose of 400 mg 12-hourly 2 dose is effective.[19, 25] Further studies of HCQ at different doses are needed.

In conclusion, our study demonstrated that rapid diagnosis and early administration of antiviral agent might prevent progression of COVID-19 to severe disease requiring oxygen supplementation or mechanical ventilation. Based on our study results, LPV/r appears to be more effective than HCQ at preventing progression to severe COVID-19 infection. We recommend a formal clinical trial of LPV/r and HCQ for patients with mild SARS-CoV2 infection.

# Abbreviations

**ARDS:** Acute Respiratory Distress Syndrome

**BMC:** Busan Medical Center

**COVID-19:** Coronavirus disease 2019

**HCQ:** Hydroxychloroquine

**HIV:** Human Immunodeficiency Virus

**IQR:** Interquartile range

**KCDC:** Korean Centers for Disease Control and Prevention

**LPV/r:** Lopinavir/ritonavir

**MERS-CoV:** Middle East Respiratory Syndrome coronavirus

**PNUH:** Pusan National University Hospital

**RNA:** Ribonucleic acid

**RT-PCR:** Real-time transcriptase-polymerase chain reaction

**SARS-CoV:** Severe Acute Respiratory Syndrome coronavirus

**SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2

**WHO:** World Health Organization

# Declarations

## Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of PNUH (IRB No. H 2003-015-089). The requirement for consent was waived by the board because of the retrospective nature of the study.

## Consent for publication

Not applicable

## Availability of data and material

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

### Funding

Not applicable.

### Author's contributions

Conceptualization: Lee S, Lee JE, Lee SO, Data collection and curation: Lee S, Lee JE, Lee SO, Heo J, Park MR, Kim DW. Formal analysis: Lee S, Lee SO. Supervision: Lee SH, Kim DK. Kim KH, Son H, Writing - original draft: Lee SO. Writing - review & editing: Lee S, Lee JE, Lee SO.

### Acknowledgements

Not applicable.

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## Tables

Table 1. Clinical Feature of Patients with SARS-CoV-2 who treated with LPV/r or hydroxychloroquine

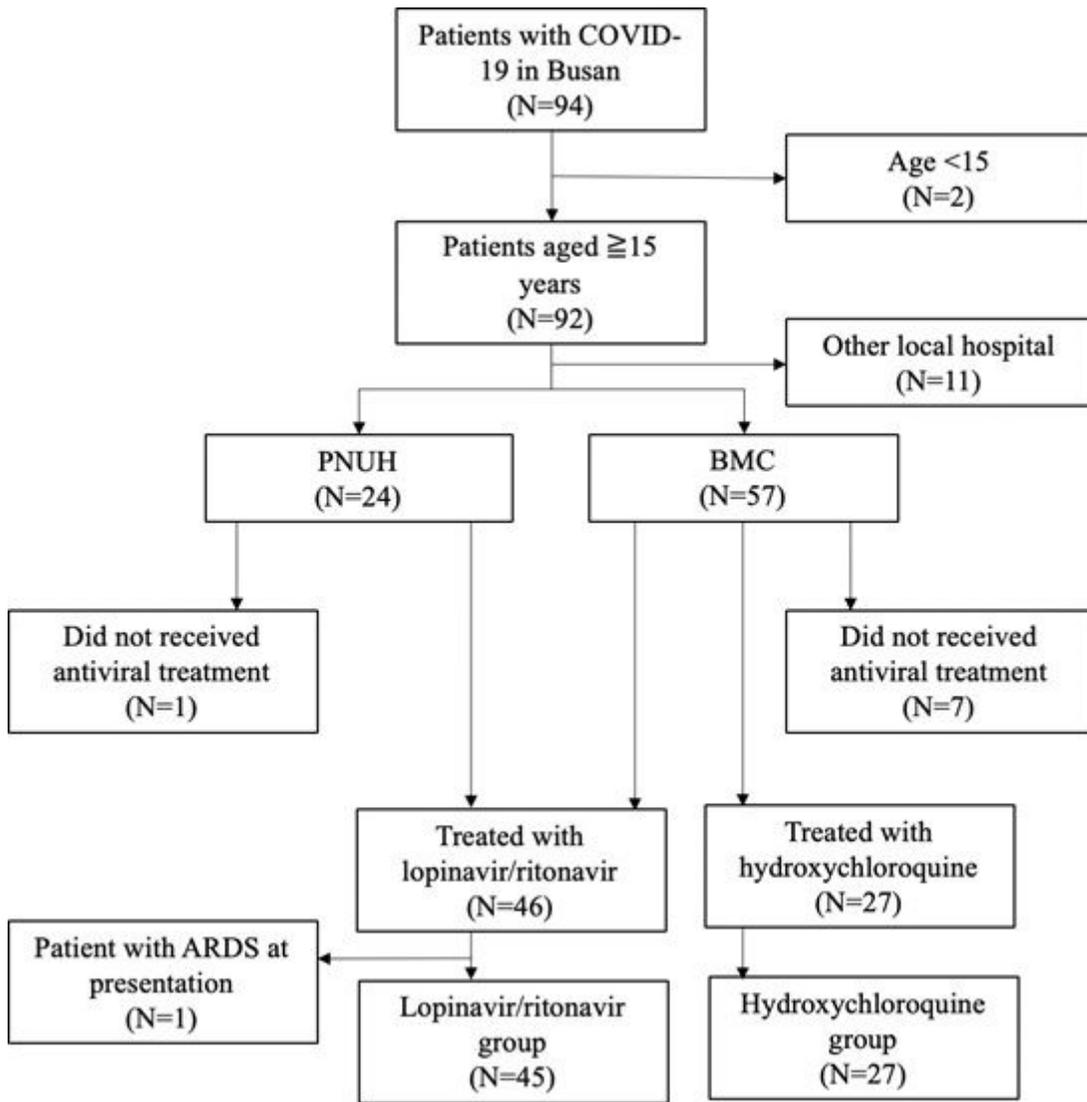
	Total (N=72)	Lopinavir/ritonavir (N=45)	Hydroxychloroquine (N=27)	P- value
Age (years), median (IQR)	37.0 (24.0-55.2)	39 (24-56)	37 (24-53)	0.58
Male sex	32 (44.4%)	20 (44%)	12 (44%)	>0.99
Symptoms				
Cough	33 (45.8%)	24 (53%)	9 (33%)	0.16
Sputum	11 (15.3%)	7 (16%)	4 (15%)	>0.99
Rhinorrhea	5 (6.9%)	3 (7%)	2 (7%)	>0.99
Nasal stuff	11 (15.3%)	6 (13%)	5 (19%)	0.80
Sore throat	20 (27.8%)	11 (24%)	9 (33%)	0.59
Febrile sense/chills	31 (43.1%)	21 (47%)	10 (37%)	0.58
Myalgia	25 (34.7%)	21 (47%)	4 (15%)	0.009
Headache	19 (26.4%)	12 (27%)	7 (26%)	>0.99
Diarrhea	2 (2.8%)	2 (4%)	0 (0%)	0.53
No Symptoms	7 (9.7%)	2 (4%)	5 (20%)	0.10
Vital signs at presentation				
Temperature (°C), median (IQR)	36.5 (36.3-37.0)	36.4 (36.3 -36.6)	36.6 (36.3 -37.0)	0.13
Systolic blood pressure (mmHg), median (IQR)	120 (110-130)	120 (110-140)	120 (110-125)	0.09
Heart rate (/min), median (IQR)	80 (74.0-87.2)	80 (76-88)	78 (72-84)	0.36
Comorbidity	9 (12.5%)	7 (16%)	2 (7%)	0.47
Cardiovascular disease	3 (4.2%)	3 (7%)	0 (0%)	0.29
Respiratory disease	3 (4.2%)	2 (4%)	1 (4%)	>0.99
Diabetes mellitus	2 (2.7%)	1 (2%)	1 (4%)	>0.99

Baseline laboratory results				
WBC × 10 <sup>9</sup> /L, median (IQR)	4.50(3.80-5.50)	4.50 (3.72 -5.42)	4.50 (4.00 -5.20)	0.79
C-reactive protein (mg/L), median (IQR)	0.235(0.078-0.758)	0.3 (0.1 -0.9)	0.1 (0.0 -0.4)	0.03
LDH (U/L), median (IQR)	183 (159-225)	186 (159-252)	178 (162-213)	0.36
WHO Class				0.008
1 (Uncomplicated illness)	46 (63.9%)	23 (51%)	23 (85%)	
2 (Mild pneumonia)	26 (36.1%)	22 (49%)	4 (15%)	

Table 2. Comparative outcome of early antiviral treatment

	All patients			Patients with uncomplicated illness		
	LPV/r (N=45)	HCQ (N=27)	P-value	LPV/r (N=23)	HCQ (N=23)	P-value
Interval from symptom onset to starting antiviral therapy (days), median (IQR)	3 (2-5)	4 (2-6)	0.742	3 (2-5)	5 (2-6)	0.57
Antiviral switching due to clinical failure within 7 days	1 (2%)	11 (40%)	<0.001	0 (0%)	10 (43%)	0.002
Disease progression during treatment	8 (18%)	12 (44%)	0.030	7 (30%)	11 (48%)	0.37
Developed pneumonia	7 (61%)	11 (41%)		7 (30%)	11 (48%)	
Developed ARDS	1 (2%)	1 (4%)		0 (0%)	0 (0%)	
Experienced adverse effects	22 (49%)	7 (26%)	0.082	13 (57%)	7 (30%)	0.14
Drug interruption due to adverse effects	2 (4%)	1 (4%)	>0.99	2 (9%)	1 (4%)	>0.99

## Figures



**Figure 1**

Distribution of patient and treatment assignment of COVID-19 patient in Busan